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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,163	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-127 and 129-133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-124,126,127 and 131-133* is/are rejected.

7)☒ Claim(s) *125, 129* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/8/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Part III: Detailed Office Action

Claims 119-127 and 129-133 are pending and under consideration.

Claims are drawn to PRO1111 protein.

The rejection of claims 119-124 and 129-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention (deposit requirement) is withdrawn in view of applicants amendment to the specification.

Formal Matters:

The new title of the invention is not acknowledged.

IDS:

The information disclosure statement, filed 11/8/2004, has been considered.

Priority Determination:

The utility for the claimed protein is active in a chondrocyte redifferentiation assay. Applicants have established that the PCT application contains the chondrocyte redifferentiation. Accordingly, priority is set at 3/30/00.

Applicants argument that priority is merited to 8/17/1998 has been fully considered but is not deemed persuasive. Applicants argue that the disclosure that PRO1111 has homology to LIG-1 provides utility. This argument has been fully considered but is not deemed persuasive because applicants have not disclosed *what* utility they feel is conferred by that identification.

Applicants have argued in the paper filed 11/8/2004 that priority is merited to at least June 23, 1999 on the basis of gene amplification. This argument has been fully considered but is not deemed persuasive for reasons cited below:

At page 10, applicants argue that both the Examiner and Sen teach that aneuploid tissues are cancerous of pre-cancerous. This argument has been fully considered but is not deemed

persuasive. Applicants statement is erroneous. Sen includes no teaching that all aneuploid tissues are cancerous or pre-cancerous, nor did the Examiner make any such statement. Rather, both Sen and the Examiner state that cancerous tissues are known to be aneuploid. It is also true that pre-cancerous tissues *may* be aneuploid. The converse is *not* true. Aneuploidy is also a feature of damaged tissue, and is commonly found in colon and lung tissues, which are subject to environmental damage. It does not invariably lead to cancer. Further, it remains that the 2-3 fold amplification of the nucleic acid is not predictive of a similar differential in protein expression; hence, the argument is not persuasive, as the claims are drawn to polypeptides, not the nucleic acids that encode them.

The Ashkenazi declaration filed under 37 CFR § 1.132 (and referred to at pages 10-11) argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene *products* (such as the claimed polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial. Contrary to the statement referred to by applicants, there has been not "significant difference relative to normal tissue" established for PRO1111 protein, nor is such predictable from a 2-3fold amplification of the nucleic acid encoding such in a minority of tested samples.

Applicants argument of the Pennica reference at page 11 of the response has been fully considered but is not deemed persuasive. Applicants have plucked a single phrase from the portion cited by the Examiner, which phrase supports their assertion of utility. However, they have taken that phrase out of context; the teachings of Pennica as a whole support the opposite conclusion, that utility of the polypeptide cannot be predicted based upon amplification of the nucleic acid, for reasons set forth at page 5 of the previous office action.

Applicant argues at pages 11-12 that the Examiner has improperly generalized the teachings of Pennica and Konopka. This argument has been fully considered but is not deemed persuasive because both references are cited to establish the state of the art, which is that it is not

predictable that a protein will be significantly amplified based upon a minor amplification of the nucleic acid encoding it. It is necessary to cite specific examples to form a general argument.

At page 12, applicants argue that the Haynes reference establishes a general trend, and that few data points deviated from the expected, and thus that Haynes shows that the data meet a "more likely than not" standard of predictability. This argument has been fully considered but is not deemed persuasive because Figure 1 of Haynes, argued by applicants, shows data correlating *protein and mRNA* levels, not genomic DNA levels and protein. Applicants have not provided any mRNA data for PRO1111. Only DNA levels are provided, no mRNA or protein levels. Accordingly, the data in the specification as filed cannot be correlated with those of Haynes. Further, the figure clearly has a tight cluster of data points showing little or not protein expression at the region corresponding to 2-3 copies of mRNA. However, the principle for which Haynes was originally cited by the Examiner still applies: Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). That is Haynes' conclusion, not the Examiner's. The 'general trend' pointed to by applicants is seen at a level of mRNA copy number that has not been established for PRO1111, nor is it predictable from the observation of 2-3 copies of *DNA* per cell.

Applicants argument at page 13 that there is expected to be a correlation between gene amplification and protein overexpression, with reference to an article by Ornoft et al., has been fully considered but is not deemed persuasive. Ornoft et al. *could only compare the levels of about 40 well-resolved and focused abundant proteins."* (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors which were not characterized on the basis of those in the Ornoft publication, and an associated rise in level of the encoded protein. The Hyman reference cited by applicants found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation

that the slight amplification of SEQ ID NO: 228 would be correlated with elevated levels of mRNA. Further, Hyman does not examine protein expression. Applicants are reminded that the instant claims are directed to proteins. Similarly, Pollack, cited by applicants, does not analyze protein levels, nor does Pollack support the assertion that it is predictable, on the basis of the minimal increase in copy number of SEQ ID NO: 228 that the protein would accordingly be found at altered levels. Accordingly, it remains that the significance of the gene amplification data is questionable, and cannot be predictably extrapolated as applying to the claimed protein. The art, taken as a whole, clearly teaches that it is not predictable that a two-fold copy increase in the nucleic acid would translate to detectable over-expression of the associated mRNA, much less any protein encoded thereby. Further, as evidenced by the Orntoft publication, the type of data presented in the instant specification clearly does not meet the standard in the art for establishing association of a protein with cancer.

At page 13, Applicant presents a discussion of the declaration by Dr. Polakis filed under 37 CFR 1.132 with the response. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1800 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 22-29, 35 and 37-41 based upon 35 U.S.C. §101 and §112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data

such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

As stated above, the Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene *products* (such as the claimed polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Applicants argue (page 15) that Hanna et al. teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested

empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Applicants arguments to the contrary fail to meet the urged "more likely than not" standard, but rather fall well within the category that significant further experimentation would be required to determine if the claimed polypeptides have the urged utility, experimentation of the type that was found to be impermissible by the court in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct,.1966).

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 132-133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein of SEQ ID NO: 229 or fragments of such that are usable for making antibodies or have chondrocyte redifferentiation activity, does not reasonably provide enablement for proteins that are encoded by a nucleic acid that is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to isolated protein at least 95% identical to SEQ ID NO:229, the extracellular domain of SEQ ID NO: 229, or SEQ ID NO: 229 without a signal sequence, which are encoded by a nucleic acid "amplified in ". For reasons stated above with regard to priority determination, the specification does not enable the use of such proteins as a cancer diagnostic, and the claims do not require that the proteins possess the sole enabled property, that of stimulating chondrocyte redifferentiation. Since chondrocyte redifferentiation is not a property that is known to be associated with genes that are amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon, and since genes that are amplified in cancers are often mutated, it is not predictable that proteins encoded by such genes will retain the enabled property.

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. As opposed to the claims, what is disclosed about PRO1111 is narrow: a single polypeptide with one potential disclosed function and no other obvious specific functions.

There are no working examples of proteins less than 100% identical SEQ ID NO:229. There is but one function potentially attributed to PRO1111 that meets the requirements of 35 U.S.C. §112, first paragraph: stimulation of chondrocyte redifferentiation. While the specification generally describes properties of cytokines, it is acknowledged that cytokines are diverse in function and structure. The specification does not provide guidance for using polypeptides related to (*i.e.*, 80%-99% identity) but not identical to SEQ ID NO:229 which do not have the single specific disclosed activity potentially shown for PRO1111. The claims are broad because they do not require the claimed nucleic acid to encode a polypeptide identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and art in terms of the diversity of proteins and lack of knowledge about function(s) of encompassed polypeptides structurally related to SEQ ID NO:229, the potential one limited working example of PRO1111 polypeptide and its one function, the lack of direction or guidance for using polypeptides that are not identical to SEQ ID NO:229, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

Claims 119-124, 126-127 and 130-133 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to proteins having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence and retain chondrocyte differentiation activity, or which are 95% identical to SEQ ID NO: 229 (or specified portions thereof), and are encoded by a nucleic acid that is amplified in adenocarcinomas or squamous cell carcinomas of the lung or in adenocarcinomas of the colon.

Claims 132-133 do not require that the claimed protein possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. The other claims have been amended to require chondrocyte redifferentiation function. The specification teaches that PRO1111 has (unspecified) homology to proteins having leucine rich repeats, for example see pages 19 and 353. The structure of the putative PRO1111 peptide is disclosed as comprising two putative transmembrane domains at page 147 of the specification; however, it is clear from the disclosure that (a) only one of the two, if any, is likely to actually *be* a transmembrane domain, (b) there is no conception of whether the protein is a type I or type II transmembrane protein, or (c) if it *is* a transmembrane protein, which end of the protein would be the 'extracellular' domain.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In this case, applicants have provided a single protein, SEQ ID NO: 229, and a single biological function, chondrocyte redifferentiation. Applicants have also provided a prophetic discussion of the protein structure, one that is internally inconsistent, and therefore cannot be relied upon. Therefore, the Examiner concludes that the breadth of the claims constitutes an invitation to experiment, rather than being supported by sufficient evidence of conception in the specification as originally filed.

Therefore, proteins comprising the sequence set forth in SEQ ID NO: 229 or active or antigenic fragments thereof but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Note that the above paragraph is reproduced verbatim from the previous Office Action. It is noted that applicants seem to have taken the above paragraph as an invitation to add the biological activity limitation to the previously pending claims. However, the above paragraph clearly indicates that it is biological active fragments of SEQ ID NO: 229 that have adequate written description (and enablement), not biologically active *variants* of such.

Applicants argument of the written description rejection at page 17 of the response filed 11/8/2004 has been fully considered but is not deemed persuasive. Applicants argue that "the specification provides detailed description about the cloning of variants and describes the gene amplification assay for testing nucleic acids in a PCR based assay." This argument has been fully considered but is not deemed persuasive because it supports the Examiner's point, that is, that the specification provides merely a "wish to know", and not an adequate written description that supports the scope of the claims. Further, applicants arguments fail to address the Examiners issues regarding the structure of the protein, as set forth at page 9, above.

Rejections Over Prior Art:

Priority is set 3/30/00. Accordingly, the rejections below are being set forth with each possible priority date in mind.

A search of the nucleic acid sequence databases revealed the following prior art:

Reference	Date	Author	Identity to SEQ ID NO:228
AI769814	12/21/99	NCI-CGAP	100% to bases 1703-2180
AI435407	3/30/99	NCI-CGAP	99.8% to bases 1743-2185
AI470931	4/13/99	NCI-CGAP	100% to bases 1795-2179
T15752	7/25/96	R. Berry et al.	100% to bases 1870-2184
U.S. Patent Number 6,689,866, SEQ ID NO: 9	3/8/00	Shimkets	99.7% to bases 1-2183
U.S. Patent Number 6,689,866, SEQ ID NO: 31	3/8/00	Shimkets	Encodes XC domain, 100% identity to SEQ ID NO : 229, residues 45-492.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 119-127, 129 and 132-133 are rejected under 35 U.S.C. 102(a) as being anticipated by Wang et al., Genbank Accession No. AF196976, cited by applicants. The sequence of Wang et al. differs from that of SEQ ID NO: 128 by only a single nucleotide, according to applicants alignment. The sequence is described as encoding "Homo sapiens tumor associated protein NAG14". The single nucleotide change is silent, that is, both sequences encode a Valine residue at that position. Cleavage of the signal sequence would automatically occur when expressing the protein in a mammalian cell. Accordingly, the claims are anticipated by Wang et al.

Claims 119-123 and 132-133 are rejected under 35 U.S.C. 102(a) as being anticipated by Jacobs et al., Genbank Accession No. AAY28806, cited by applicants. The sequence of Jacobs et al. differs from that of SEQ ID NO: 129 by only a single amino acid, according to applicants alignment. Accordingly, the claims are anticipated by Jacobs et al.

Claims 119-123, and 130-133 are rejected under 35 U.S.C. 102(a) as being anticipated by Jacobs, WO 99/50405. SEQ ID NO: 2 of the publication is 99.7% identical to SEQ ID NO: 229 of the instant application. Fusion proteins, including to epitope tags, are disclosed at page 54. The reference is silent with respect to whether or not the nucleic acid encodes a protein with chondrocyte redifferentiation activity. Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Applicants arguments regarding the priority date of the application have been fully considered but are not deemed persuasive for reasons cited above with respect to the priority determination.

Claims 119-124, 127, and 130-133 are rejected under 35 U.S.C. 102(e) as being anticipated by Shimkets, U.S. Patent Number 6,689,866 or US Patent Application Publication US2003/0054514 A1, or US Patent Application Publication US2003/0003532 A1. The US Patent Application Publications are divisionals of the patent, and differ only in the claims. The '514 publication contains claims to nucleic acids, proteins (see claim 11), and antibodies (see claim 13), and the '532 application contains claims to nucleic acids and vectors. The teachings will be discussed with reference to the issued patent. SEQ ID NO: 9 of the patent is 99.7% identical to SEQ ID NO: 228 of the instant application, at bases 1-2183 (bases 159-2341 of the patent), and encodes a protein 99.2% identical to that of SEQ ID NO: 229. SEQ ID NO: 31 is a fragment of SEQ ID NO: 9, is identified as encoding the extracellular domain (see figures 17A and 17B), which is 100% identical to residues 45-495 of SEQ ID NO: 229. Fusion proteins, including Ig fusions, are disclosed beginning at column 32, line 50.

Accordingly, the claims are anticipated by Shimkets.

Applicants arguments regarding the priority date of the application have been fully considered but are not deemed persuasive for reasons cited above with respect to the priority determination.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 119-123, 130 and 132-133 are rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al.

The teachings of the primary references are summarized in the Table above. Each has over 99% identity to SEQ ID NO: 228 over the full length of the locus from the database. As sequence identity is calculated relative to the shorter of the two sequences being compared, the proteins encoded by the sequences would meet the limitations of claims 119-123 and 131-132.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13. Fusion proteins are disclosed at page 8 as being useful for purification of the encoded protein.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA's disclosed by any one of the primary references to express and then isolate the encoded polypeptide as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above.

Applicants argument that ESTs are not enabling disclosures since they provide no utility has been fully considered but is not deemed persuasive. Utility as defined by 35 U.S.C. §101 is not required for a finding of obviousness. The EST disclosures disclose and enable one of ordinary skill in the art to make the DNAs disclosed therein. Sibson provides the motivation to express such sequences. Accordingly, the invention as claimed is *prima facie* obvious.

Claim 131 is any one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al. and further in view of Capon et al., U.S. Patent Number 5,116,964 for reasons of record in the previous Office action. Applicants have presented no further argument of this rejection.

Claims 130 and 131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al., Genbank Accession No. AF196976, cited by applicants, in view of Capon et al., U.S. Patent Number 5,116,964 for reasons of record in the previous Office action for reasons cited with respect to claim 131 in the rejection over one of Loci AI769814, AI435407 , AI470931, or T15752, in view of Sibson et al. and further in view of Capon et al., U.S. Patent Number 5,116,964 in the previous Office Action.

Advisory Information:

Claims 125 and 129 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector

~~Lorr~~aine Spector, Ph.D.
Primary Examiner